

## APPENDIX A

### SUMMARY OF LESIONS IN REGIMEN A FEMALE MICE IN THE 2-YEAR GAVAGE STUDY OF CHLORAL HYDRATE

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TABLE A1

Summary of the Incidence of Neoplasms in Regimen A Female Mice in the 2-Year Gavage Study of Chloral Hydrate<sup>a</sup>

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
<b>Disposition Summary</b>				
Animals initially in study	48	48	48	48
Early deaths				
Accidental deaths			1	1
Moribund	2	4	3	2
Natural deaths	9	5	1	9
Survivors				
Died last week of study		1		
Terminal sacrifice	37	38	43	36
Animals examined microscopically	48	48	48	48
<b>Alimentary System</b>				
Gallbladder	(46)	(8)	(4)	(47)
Lymphoma malignant				1 (2%)
Intestine large, cecum	(42)	(6)	(3)	(41)
Lymphoma malignant	1 (2%)			
Intestine large, colon	(46)	(9)	(3)	(43)
Lymphoma malignant	2 (4%)			
Intestine large, rectum	(44)	(8)	(3)	(43)
Lymphoma malignant				1 (2%)
Intestine small	(41)	(7)	(6)	(42)
Lymphoma malignant			1 (17%)	
Intestine small, duodenum	(40)	(7)	(4)	(42)
Polyp adenomatous				1 (2%)
Intestine small, ileum	(40)	(6)	(3)	(39)
Lymphoma malignant				1 (3%)
Intestine small, jejunum	(41)	(6)	(5)	(41)
Hemangioma			1 (20%)	
Lymphoma malignant	2 (5%)			1 (2%)
Liver	(48)	(48)	(48)	(48)
Hepatocellular adenoma	1 (2%)	2 (4%)	3 (6%)	2 (4%)
Hepatocellular carcinoma	1 (2%)			1 (2%)
Histiocytic sarcoma	1 (2%)	1 (2%)		3 (6%)
Lymphoma malignant	6 (13%)	5 (10%)	1 (2%)	6 (13%)
Mesentery	(1)	(1)	(1)	(1)
Lymphoma malignant	1 (100%)			
Pancreas	(48)	(8)	(5)	(46)
Fibrosarcoma	1 (2%)			
Lymphoma malignant	2 (4%)	1 (13%)		3 (7%)
Salivary glands	(48)	(10)	(5)	(48)
Lymphoma malignant	3 (6%)		1 (20%)	3 (6%)
Stomach, forestomach	(47)	(10)	(4)	(45)
Papilloma squamous				1 (2%)
Stomach, glandular	(47)	(10)	(4)	(46)
Lymphoma malignant				1 (2%)
Tongue	(48)	(9)	(5)	(48)
Lymphoma malignant				1 (2%)
Papilloma squamous	1 (2%)			
<b>Cardiovascular System</b>				
Heart	(48)	(10)	(5)	(48)
Histiocytic sarcoma	1 (2%)			1 (2%)
Lymphoma malignant	1 (2%)			1 (2%)

**TABLE A1****Summary of the Incidence of Neoplasms in Regimen A Female Mice in the 2-Year Gavage Study of Chloral Hydrate**

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
<b>Endocrine System</b>				
Adrenal gland, cortex	(46)	(9)	(5)	(47)
Histiocytic sarcoma		1 (11%)		
Lymphoma malignant	1 (2%)			2 (4%)
Adrenal gland, medulla	(46)	(9)	(3)	(46)
Lymphoma malignant	1 (2%)			1 (2%)
Pheochromocytoma malignant	1 (2%)			
Islets, pancreatic	(48)	(8)	(5)	(46)
Adenoma				2 (4%)
Pituitary gland	(45)	(44)	(47)	(41)
Adenoma, pars distalis		2 (5%)		5 (12%)
Adenoma, pars intermedia	2 (4%)			
Thyroid gland	(47)	(9)	(5)	(48)
Lymphoma malignant				1 (2%)
<b>General Body System</b>				
Tissue NOS	(1)			
Lymphoma malignant, fat	1 (100%)			
<b>Genital System</b>				
Clitoral gland	(43)	(8)	(4)	(43)
Lymphoma malignant				2 (5%)
Ovary	(48)	(29)	(21)	(46)
Cystadenoma	1 (2%)		1 (5%)	2 (4%)
Histiocytic sarcoma	1 (2%)			2 (4%)
Luteoma	1 (2%)			
Lymphoma malignant	2 (4%)	1 (3%)		2 (4%)
Lymphoma malignant, periovarian tissue	1 (2%)			3 (7%)
Uterus	(48)	(26)	(29)	(47)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma	2 (4%)	1 (4%)		3 (6%)
Leiomyoma			1 (3%)	
Lymphoma malignant				2 (4%)
Polyp	1 (2%)			
Vagina	(48)	(9)	(5)	(45)
Histiocytic sarcoma	2 (4%)			4 (9%)
Lymphoma malignant	2 (4%)			1 (2%)
Polyp				2 (4%)
<b>Hematopoietic System</b>				
Bone marrow	(47)	(10)	(5)	(47)
Hemangiosarcoma	1 (2%)			1 (2%)
Lymphoma malignant	3 (6%)			2 (4%)
Lymph node	(48)	(13)	(8)	(47)
Fibrosarcoma, inguinal		1 (8%)		
Histiocytic sarcoma, lumbar	1 (2%)			
Lymphoma malignant				1 (2%)
Lymphoma malignant, axillary		1 (8%)		
Lymphoma malignant, deep cervical			1 (13%)	
Lymphoma malignant, inguinal				1 (2%)
Lymphoma malignant, lumbar	2 (4%)	1 (8%)	1 (13%)	2 (4%)
Lymphoma malignant, mediastinal	1 (2%)	2 (15%)		
Lymphoma malignant, renal	1 (2%)	1 (8%)	2 (25%)	1 (2%)

TABLE A1

Summary of the Incidence of Neoplasms in Regimen A Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
<b>Hematopoietic System</b> (continued)				
Lymph node, mandibular	(47)	(11)	(5)	(46)
Lymphoma malignant	4 (9%)	3 (27%)	2 (40%)	6 (13%)
Lymph node, mesenteric	(46)	(9)	(7)	(44)
Histiocytic sarcoma	1 (2%)	1 (11%)		1 (2%)
Lymphoma malignant	6 (13%)	4 (44%)	2 (29%)	9 (20%)
Spleen	(47)	(14)	(19)	(47)
Hemangiosarcoma	1 (2%)		1 (5%)	2 (4%)
Lymphoma malignant	8 (17%)	6 (43%)	7 (37%)	12 (26%)
Thymus	(41)	(5)	(5)	(44)
Lymphoma malignant	3 (7%)	1 (20%)	2 (40%)	6 (14%)
<b>Integumentary System</b>				
Mammary gland	(44)	(6)	(5)	(44)
Adenocarcinoma			1 (20%)	1 (2%)
Adenoma		1 (17%)		
Fibrosarcoma	1 (2%)			
Lymphoma malignant	1 (2%)			
Skin	(45)	(10)	(5)	(46)
Fibrosarcoma				2 (4%)
Hemangiosarcoma	1 (2%)			2 (4%)
Histiocytic sarcoma		1 (10%)		
Lymphoma malignant	1 (2%)			
Osteosarcoma, metastatic, bone		1 (10%)		
<b>Musculoskeletal System</b>				
Bone	(47)	(10)	(5)	(48)
Osteosarcoma, lumbar, vertebra		1 (10%)		
Skeletal muscle	(48)	(11)	(5)	(48)
Fibrosarcoma		2 (18%)		
Lymphoma malignant				1 (2%)
<b>Nervous System</b>				
None				
<b>Respiratory System</b>				
Lung	(48)	(48)	(48)	(48)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)	2 (4%)	4 (8%)
Histiocytic sarcoma	1 (2%)	1 (2%)		2 (4%)
Lymphoma malignant	4 (8%)	4 (8%)	1 (2%)	9 (19%)
Osteosarcoma, metastatic, bone		1 (2%)		
Osteosarcoma, metastatic, uncertain primary site				1 (2%)
Trachea	(47)	(9)	(4)	(46)
Lymphoma malignant				1 (2%)

**TABLE A1****Summary of the Incidence of Neoplasms in Regimen A Female Mice in the 2-Year Gavage Study of Chloral Hydrate**

	<b>Vehicle Control</b>	<b>25 mg/kg</b>	<b>50 mg/kg</b>	<b>100 mg/kg</b>
<b>Special Senses System</b>				
Harderian gland	(48)	(10)	(6)	(47)
Adenoma	2 (4%)	1 (10%)		2 (4%)
Carcinoma	1 (2%)			
Lymphoma malignant	2 (4%)		1 (17%)	2 (4%)
Lacrimal gland	(41)	(6)	(4)	(40)
Lymphoma malignant	1 (2%)			1 (3%)
<b>Urinary System</b>				
Kidney	(48)	(10)	(5)	(48)
Histiocytic sarcoma	1 (2%)			
Lymphoma malignant	6 (13%)	2 (20%)		8 (17%)
Urinary bladder	(47)	(10)	(5)	(43)
Lymphoma malignant	3 (6%)		3	(7%)
<b>Neoplasm Summary</b>				
Total animals with primary neoplasms <sup>b</sup>	21	18	17	33
Total primary neoplasms	102	49	32	144
Total animals with benign neoplasms	8	6	8	16
Total benign neoplasms	10	7	8	21
Total animals with malignant neoplasms	16	12	10	23
Total malignant neoplasms	92	42	24	123
Total animals with metastatic neoplasms		1		1
Total metastatic neoplasms		2		1

<sup>a</sup> Number of animals examined microscopically at the site and the number of animals with neoplasm

<sup>b</sup> Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2

## Statistical Analysis of Primary Neoplasms in Regimen A Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
<b>Liver: Hepatocellular Adenoma</b>				
Overall rate <sup>a</sup>	1/48 (2%)	2/48 (4%)	3/48 (6%)	2/48 (4%)
Adjusted rate <sup>b</sup>	2.3%	4.5%	6.4%	4.7%
Terminal rate <sup>c</sup>	1/37 (3%)	1/39 (3%)	3/43 (7%)	2/36 (6%)
First incidence (days)	757 (T)	752	757 (T)	757 (T)
Poly-3 test <sup>d</sup>	P=0.4037	P=0.5155	P=0.3379	P=0.5027
<b>Liver: Hepatocellular Adenoma or Carcinoma</b>				
Overall rate	2/48 (4%)	2/48 (4%)	3/48 (6%)	3/48 (6%)
Adjusted rate	4.7%	4.5%	6.4%	7.0%
Terminal rate	2/37 (5%)	1/39 (3%)	3/43 (7%)	3/36 (8%)
First incidence (days)	757 (T)	752	757 (T)	757 (T)
Poly-3 test	P=0.3708	P=0.6779N	P=0.5403	P=0.5035
<b>Lung: Alveolar/Bronchiolar Adenoma</b>				
Overall rate	1/48 (2%)	1/48 (2%)	2/48 (4%)	4/48 (8%)
Adjusted rate	2.3%	2.2%	4.3%	9.4%
Terminal rate	1/37 (3%)	1/39 (3%)	2/43 (5%)	4/36 (11%)
First incidence (days)	757 (T)	757 (T)	757 (T)	757 (T)
Poly-3 test	P=0.0711	P=0.7508N	P=0.5308	P=0.1805
<b>Pituitary Gland (Pars Distalis): Adenoma</b>				
Overall rate	0/45 (0%)	2/44 (5%)	0/47 (0%)	5/41 (12%)
Adjusted rate	0.0%	4.7%	0.0%	13.3%
Terminal rate	0/36 (0%)	1/38 (3%)	0/42 (0%)	5/32 (16%)
First incidence (days)	— <sup>e</sup>	700	— <sup>f</sup>	757 (T)
Poly-3 test	P=0.0073	P=0.2473	—	P=0.0237
<b>Skin: Fibrosarcoma, Hemangiosarcoma, or Histiocytic Sarcoma</b>				
Overall rate	1/45 (2%)	1/10 (10%)	0/5 (0%)	4/46 (9%)
Adjusted rate	2.4%	14.9%	0.0%	9.6%
Terminal rate	1/37 (3%)	0/1 (0%)	0/0	3/36 (8%)
First incidence (days)	757 (T)	737	—	692
Poly-3 test	(NA)	— <sup>g</sup>	— <sup>g</sup>	P=0.1867
<b>All Organs: Histiocytic Sarcoma</b>				
Overall rate	3/48 (6%)	2/48 (4%)	0/48 (0%)	5/48 (10%)
Adjusted rate	7.0%	4.4%	0.0%	11.4%
Terminal rate	2/37 (5%)	0/39 (0%)	0/43 (0%)	2/36 (6%)
First incidence (days)	681	638	—	567
Poly-3 test	P=0.2238	P=0.4781N	P=0.1046N	P=0.3698
<b>All Organs: Malignant Lymphoma</b>				
Overall rate	9/48 (19%)	7/48 (15%)	8/48 (17%)	15/48 (31%)
Adjusted rate	20.5%	15.3%	17.1%	34.1%
Terminal rate	4/37 (11%)	4/39 (10%)	7/43 (16%)	11/36 (31%)
First incidence (days)	605	622	722 (T)	555
Poly-3 test	P=0.0455	P=0.3571N	P=0.4432N	P=0.1210

TABLE A2

## Statistical Analysis of Primary Neoplasms in Regimen A Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
<b>All Organs: Benign Neoplasms</b>				
Overall rate	8/48 (17%)	6/48 (13%)	8/48 (17%)	16/48 (33%)
Adjusted rate	18.3%	13.4%	17.2%	37.5%
Terminal rate	6/37 (16%)	4/39 (10%)	8/43 (19%)	15/36 (42%)
First incidence (days)	551	700	757 (T)	747
Poly-3 test	P=0.0092	P=0.3652N	P=0.5505N	P=0.0404
<b>All Organs: Malignant Neoplasms</b>				
Overall rate	16/48 (33%)	12/48 (25%)	10/48 (21%)	23/48 (48%)
Adjusted rate	36.0%	25.7%	21%	51%
Terminal rate	9/37 (24%)	6/39 (15%)	9/43 (21%)	15/36 (42%)
First incidence (days)	605	564	722 (T)	555
Poly-3 test	P=0.0417	P=0.2006N	P=0.0948N	P=0.1194
<b>All Organs: Benign or Malignant Neoplasms</b>				
Overall rate	21/48 (44%)	18/48 (38%)	17/48 (35%)	33/48 (69%)
Adjusted rate	46.6%	38.3%	36.4%	73.0%
Terminal rate	13/37 (35%)	10/39 (26%)	16/43 (37%)	25/36 (69%)
First incidence (days)	551	564	722 (T)	555
Poly-3 test	P=0.0024	P=0.2774N	P=0.2192N	P=0.0093

(T)Terminal sacrifice

(NA)Not applicable

- a Number of neoplasm-bearing animals/number of animals with tissue examined microscopically
- b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
- c Observed incidence at terminal kill
- d Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A lower incidence in a dose group is indicated by N.
- e Not applicable; no neoplasms in animal group
- f Value of statistic cannot be computed.
- g Tissue was examined microscopically only when it was observed to be abnormal at necropsy; thus, statistical comparisons with the vehicle controls are not appropriate.

**TABLE A3a****Historical Incidence of Pituitary Gland Pars Distalis Neoplasms in Control Female B6C3F<sub>1</sub>/Nctr BR Mice<sup>a</sup>**

<b>Study</b>	<b>Adenoma or Carcinoma</b>
Doxylamine	2/38
Fumonisin B <sub>1</sub>	0/29
Pyrilamine	2/45
Sulfamethazine	10/158
Tripolidine	1/38
Total (%)	15/308 (4.9%)
Mean $\bar{x}$ standard deviation	3.7% $\bar{x}$ 2.5%
Range	0%-6%

<sup>a</sup> Data as of September 1999. Studies were conducted at the National Center for Toxicological Research in animals given NIH-31 feed.

**TABLE A3b****Historical Incidence of Malignant Lymphoma in Control Female B6C3F<sub>1</sub>/Nctr BR Mice<sup>a</sup>**

<b>Study</b>	<b>Incidence in Controls</b>
Doxylamine	13/48
Fumonisin B <sub>1</sub>	20/47
Pyrilamine	10/48
Sulfamethazine	39/184
Tripolidine	10/47
Total (%)	92/374 (24.6%)
Mean $\bar{x}$ standard deviation	26.6% $\bar{x}$ 9.3%
Range	21%-43%

<sup>a</sup> Data as of September 1999. Studies were conducted at the National Center for Toxicological Research in animals given NIH-31 feed. Includes data for histiocytic, lymphocytic, mixed, unspecified, or undifferentiated cell type lymphomas



**TABLE A3c****Historical Incidence of Alveolar/bronchiolar Neoplasms in Control Female B6C3F<sub>1</sub>/Nctr BR Mice<sup>a</sup>**

<b>Study</b>	<b>Adenoma</b>	<b>Incidence in Controls Carcinoma</b>	<b>Adenoma or Carcinoma</b>
Doxylamine	3/48	0/48	3/48
Fumonisin B <sub>1</sub>	2/47	0/47	2/47
Pyrilamine	1/48	0/48	1/48
Sulfamethazine	5/182	1/182	6/182
Tripolidine	3/47	2/47	5/47
Total (%)	14/372 (3.8%)	3/372 (0.8%)	17/372 (4.6%)
Mean $\pm$ standard deviation	4.4% $\pm$ 2.0%	1.0% $\pm$ 1.9%	5.3% $\pm$ 3.3%
Range	2%-6%	0%-4%	2%-11%

<sup>a</sup> Data as of September 1999. Studies were conducted at the National Center for Toxicological Research in animals given NIH-31 feed.

**TABLE A3d****Historical Incidence of Hepatocellular Neoplasms in Control Female B6C3F<sub>1</sub>/Nctr BR Mice<sup>a</sup>**

<b>Study</b>	<b>Adenoma</b>	<b>Incidence in Controls Carcinoma</b>	<b>Adenoma or Carcinoma</b>
Doxylamine	0/46	0/46	0/46
Fumonisin B <sub>1</sub>	5/47	0/47	5/47
Pyrilamine	1/47	0/47	1/47
Sulfamethazine	8/184	2/184	10/184
Tripolidine	2/47	2/47	4/47
Total (%)	16/371 (4.3%)	4/371 (1.1%)	20/371 (5.4%)
Mean $\pm$ standard deviation	4.3% $\pm$ 4.0%	1.1% $\pm$ 1.9%	5.3% $\pm$ 4.4%
Range	0%-11%	0%-4%	0%-11%

<sup>a</sup> Data as of September 1999. Studies were conducted at the National Center for Toxicological Research in animals given NIH-31 feed.

TABLE A4

**Summary of the Incidence of Nonneoplastic Lesions in Regimen A Female Mice in the 2-Year Gavage Study of Chloral Hydrate<sup>a</sup>**

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
<b>Disposition Summary</b>				
Animals initially in study	48	48	48	48
Early deaths				
Accidental deaths			1	1
Moribund	2	4	3	2
Natural deaths	9	5	1	9
Survivors				
Died last week of study		1		
Terminal sacrifice	37	38	43	36
Animals examined microscopically	48	48	48	48
<b>Alimentary System</b>				
Esophagus	(47)	(9)	(4)	(44)
Hyperkeratosis	1 (2%)			1 (2%)
Ulcer	1 (2%)			
Gallbladder	(46)	(8)	(4)	(47)
Infiltration cellular, lymphocytic	4 (9%)			4 (9%)
Intestine large, cecum	(42)	(6)	(3)	(41)
Hyperplasia, lymphoid	5 (12%)			4 (10%)
Intestine large, rectum	(44)	(8)	(3)	(43)
Erosion	2 (5%)			
Hyperplasia, lymphoid				1 (2%)
Intestine small, duodenum	(40)	(7)	(4)	(42)
Inflammation				1 (2%)
Intestine small, ileum	(40)	(6)	(3)	(39)
Hyperplasia, lymphoid	2 (5%)			1 (3%)
Inflammation				1 (3%)
Intestine small, jejunum	(41)	(6)	(5)	(41)
Inflammation				1 (2%)
Liver	(48)	(48)	(48)	(48)
Angiectasis		2 (4%)		
Basophilic focus	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Clear cell focus		1 (2%)		
Congestion				1 (2%)
Cyst, bile duct			1 (2%)	
Degeneration			1 (2%)	
Eosinophilic focus		1 (2%)	4 (8%)	1 (2%)
Hematopoietic cell proliferation	3 (6%)	13 (27%)	16 (33%)	4 (8%)
Infiltration cellular, lymphocytic	33 (69%)	35 (73%)	40 (83%)	36 (75%)
Inflammation	2 (4%)			1 (2%)
Mineralization				1 (2%)
Necrosis	32 (67%)	35 (73%)	31 (65%)	32 (67%)
Necrosis, coagulative	1 (2%)		2 (4%)	
Regeneration			1 (2%)	
Tension lipoidosis	17 (35%)	13 (27%)	16 (33%)	16 (33%)
Vacuolization cytoplasmic	26 (54%)	36 (75%)	30 (63%)	23 (48%)
Mesentery	(1)	(1)	(1)	(1)
Necrosis, fat		1 (100%)	1 (100%)	1 (100%)

<sup>a</sup> Number of animals examined microscopically at the site and the number of animals with lesion

**TABLE A4**  
**Summary of the Incidence of Nonneoplastic Lesions in Regimen A Female Mice in the 2-Year Gavage Study of Chloral Hydrate**

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
<b>Alimentary System</b> (continued)				
Pancreas	(48)	(8)	(5)	(46)
Atrophy	1 (2%)	1 (13%)		
Ectasia, duct				1 (2%)
Focal cellular change	2 (4%)		2 (40%)	2 (4%)
Infiltration cellular, lymphocytic	26 (54%)	3 (38%)	2 (40%)	19 (41%)
Polyarteritis			1 (20%)	
Salivary glands	(48)	(10)	(5)	(48)
Atrophy				2 (4%)
Hyperplasia, duct	1 (2%)			
Infiltration cellular, lymphocytic	38 (79%)	6 (60%)	4 (80%)	41 (85%)
Polyarteritis			1 (20%)	
Stomach, forestomach	(47)	(10)	(4)	(45)
Hyperkeratosis		3 (30%)		2 (4%)
Ulcer		1 (10%)		
Stomach, glandular	(47)	(10)	(4)	(46)
Crystals	1 (2%)			
Cyst	2 (4%)		1 (25%)	3 (7%)
Degeneration, hyaline	1 (2%)			
Mineralization		1 (10%)		2 (4%)
Tongue	(48)	(9)	(5)	(48)
Infiltration cellular, mast cell	2 (4%)			
Inflammation		1 (11%)		
Polyarteritis	1 (2%)		1 (20%)	
<b>Cardiovascular System</b>				
Blood vessel, aorta	(42)	(8)	(5)	(45)
Mineralization		1 (13%)		
Heart	(48)	(10)	(5)	(48)
Degeneration	1 (2%)	1 (10%)		
Dilatation		1 (10%)		
Infiltration cellular, lymphocytic				2 (4%)
Inflammation	1 (2%)			1 (2%)
Polyarteritis	1 (2%)			1 (2%)
Thrombus	1 (2%)			
<b>Endocrine System</b>				
Adrenal gland	(46)	(9)	(5)	(47)
Accessory adrenal cortical nodule	1 (2%)			1 (2%)
Adrenal gland, cortex	(46)	(9)	(5)	(47)
Ectopic tissue	1 (2%)			2 (4%)
Hyperplasia				1 (2%)
Hyperplasia, spindle cell	43 (93%)	6 (67%)	2 (40%)	44 (94%)
Thrombus	1 (2%)			
Vacuolization cytoplasmic	2 (4%)			
Adrenal gland, medulla	(46)	(9)	(3)	(46)
Hyperplasia				2 (4%)
Vacuolization cytoplasmic	1 (2%)			1 (2%)
Islets, pancreatic	(48)	(8)	(5)	(46)
Hyperplasia			1 (20%)	1 (2%)

TABLE A4

**Summary of the Incidence of Nonneoplastic Lesions in Regimen A Female Mice in the 2-Year Gavage Study of Chloral Hydrate**

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
<b>Endocrine System</b> (continued)				
Parathyroid gland	(38)	(9)	(3)	(40)
Cyst				1 (3%)
Ectopic thymus	1 (3%)			2 (5%)
Infiltration cellular, lymphocytic	1 (3%)			1 (3%)
Vacuolization cytoplasmic	1 (3%)			1 (3%)
Pituitary gland	(45)	(44)	(47)	(41)
Angiectasis		1 (2%)	2 (4%)	1 (2%)
Degeneration, cystic, pars distalis		2 (5%)	1 (2%)	
Hemorrhage				1 (2%)
Hyperplasia, pars distalis	4 (9%)	6 (14%)	4 (9%)	9 (22%)
Thyroid gland	(47)	(9)	(5)	(48)
Crystals				1 (2%)
Cyst, follicle		1 (11%)		
Degeneration	1 (2%)	1 (11%)		1 (2%)
Ectopic thymus				1 (2%)
Hyperplasia, follicular cell		1 (11%)		2 (4%)
Infiltration cellular, lymphocytic	4 (9%)			
Polyarteritis			1 (20%)	
Ultimobranchial cyst	11 (23%)	2 (22%)	1 (20%)	10 (21%)
<b>General Body System</b>				
None				
<b>Genital System</b>				
Clitoral gland	(43)	(8)	(4)	(43)
Atrophy	40 (93%)	6 (75%)	4 (100%)	38 (88%)
Ovary	(48)	(29)	(21)	(46)
Atrophy	39 (81%)	7 (24%)	1 (5%)	35 (76%)
Congestion	1 (2%)			
Cyst	10 (21%)	15 (52%)	13 (62%)	14 (30%)
Cyst, periovarian tissue	16 (33%)	5 (17%)	4 (19%)	15 (33%)
Hematocyst	7 (15%)	3 (10%)	2 (10%)	3 (7%)
Hyperplasia, adenomatous	2 (4%)		1 (5%)	1 (2%)
Hyperplasia, tubular				2 (4%)
Infiltration cellular, lymphocytic	5 (10%)			2 (4%)
Mineralization		1 (3%)		1 (2%)
Polyarteritis				1 (2%)
Uterus	(48)	(26)	(29)	(47)
Angiectasis	1 (2%)		1 (3%)	1 (2%)
Atrophy	2 (4%)	5 (19%)	3 (10%)	2 (4%)
Dilatation	2 (4%)	2 (8%)	2 (7%)	
Fibrosis	1 (2%)	1 (4%)	1 (3%)	1 (2%)
Hyperplasia, cystic, endometrium	37 (77%)	16 (62%)	23 (79%)	37 (79%)
Hypertrophy, myometrium				2 (4%)
Inflammation		1 (4%)		
Metaplasia, squamous				1 (2%)
Prolapse	1 (2%)			1 (2%)
Vagina	(48)	(9)	(5)	(45)
Atrophy	2 (4%)	4 (44%)	2 (40%)	3 (7%)
Dysplasia	1 (2%)	1 (11%)		2 (4%)
Infiltration cellular, lymphocytic	3 (6%)			2 (4%)

TABLE A4

## Summary of the Incidence of Nonneoplastic Lesions in Regimen A Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
<b>Hematopoietic System</b>				
Bone marrow	(47)	(10)	(5)	(47)
Hyperplasia	3 (6%)	5 (50%)		6 (13%)
Lymph node	(48)	(13)	(8)	(47)
Hematopoietic cell proliferation				1 (2%)
Hematopoietic cell proliferation, inguinal				1 (2%)
Hemorrhage, inguinal				1 (2%)
Hyperplasia, lymphoid, inguinal			1 (13%)	
Hyperplasia, lymphoid, thoracic			1 (13%)	
Infiltration cellular, histiocytic, inguinal				1 (2%)
Lymph node, mandibular	(47)	(11)	(5)	(46)
Hematopoietic cell proliferation				1 (2%)
Hemorrhage	3 (6%)	3 (27%)		
Hyperplasia, lymphoid	7 (15%)	1 (9%)	1 (20%)	9 (20%)
Hyperplasia, plasma cell				1 (2%)
Infiltration cellular, histiocytic		1 (9%)		
Lymph node, mesenteric	(46)	(9)	(7)	(44)
Atrophy	2 (4%)	2 (22%)		1 (2%)
Hematopoietic cell proliferation				1 (2%)
Hemorrhage	4 (9%)		1 (14%)	2 (5%)
Hyperplasia, lymphoid	2 (4%)	1 (11%)	2 (29%)	2 (5%)
Infiltration cellular, histiocytic				1 (2%)
Polyarteritis, artery			1 (14%)	
Spleen	(47)	(14)	(19)	(47)
Atrophy	2 (4%)	2 (14%)		1 (2%)
Congestion		1 (7%)		3 (6%)
Hematopoietic cell proliferation	4 (9%)	3 (21%)	5 (26%)	9 (19%)
Hyperplasia, lymphoid	13 (28%)	4 (29%)	5 (26%)	11 (23%)
Infiltration cellular, lymphocytic				1 (2%)
Infiltration cellular, plasma cell				1 (2%)
Inflammation				1 (2%)
Thymus	(41)	(5)	(5)	(44)
Atrophy, cortex	30 (73%)	3 (60%)	3 (60%)	34 (77%)
Congestion	1 (2%)			
Cyst				1 (2%)
Ectopic parathyroid gland	1 (2%)			1 (2%)
Hyperplasia, lymphoid, medulla	14 (34%)	1 (20%)		17 (39%)
Inflammation		1 (20%)		
<b>Integumentary System</b>				
Mammary gland	(44)	(6)	(5)	(44)
Hyperplasia	1 (2%)	1 (17%)		7 (16%)
Inflammation	1 (2%)			
Lactation	4 (9%)	1 (17%)		1 (2%)
Skin	(45)	(10)	(5)	(46)
Edema		1 (10%)		

TABLE A4

**Summary of the Incidence of Nonneoplastic Lesions in Regimen A Female Mice in the 2-Year Gavage Study of Chloral Hydrate**

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
<b>Musculoskeletal System</b>				
Bone, femur	(47)	(10)	(5)	(47)
Degeneration, cartilage				1 (2%)
Fibrous osteodystrophy	18 (38%)			10 (21%)
Polyarteritis			1 (20%)	
Bone, sternum	(47)	(10)	(5)	(48)
Fibrous osteodystrophy, multifocal	36 (77%)	3 (30%)		33 (69%)
Skeletal muscle	(48)	(11)	(5)	(48)
Infiltration cellular, lymphocytic	2 (4%)	1 (9%)		1 (2%)
Polyarteritis	1 (2%)			
<b>Nervous System</b>				
Brain, cerebellum	(48)	(10)	(5)	(48)
Degeneration	1 (2%)			
Thrombus	1 (2%)			
Brain, cerebrum	(48)	(10)	(5)	(48)
Degeneration	1 (2%)			
Mineralization, multifocal, thalamus	28 (58%)	3 (30%)	1 (20%)	22 (46%)
Polyarteritis			1 (20%)	
Thrombus	1 (2%)			
Spinal cord, thoracic	(48)	(10)	(5)	(47)
Degeneration	1 (2%)			
Developmental malformation				1 (2%)
Infiltration cellular, lymphocytic				1 (2%)
Thrombus	1 (2%)			
<b>Respiratory System</b>				
Larynx	(44)	(5)	(1)	(43)
Infiltration cellular, lymphocytic	1 (2%)			
Inflammation		1 (20%)		1 (2%)
Lung	(48)	(48)	(48)	(48)
Foreign body	1 (2%)			
Hemorrhage	2 (4%)		1 (2%)	
Hyperplasia, alveolar epithelium				1 (2%)
Hyperplasia, alveolus		1 (2%)		
Infiltration cellular, histiocytic		2 (4%)	2 (4%)	1 (2%)
Infiltration cellular, lymphocytic	37 (77%)	24 (50%)	29 (60%)	29 (60%)
Inflammation	4 (8%)			2 (4%)
Leukocytosis		1 (2%)		
Mineralization		1 (2%)		
Thrombus	1 (2%)	2 (4%)	1 (2%)	
Nose	(47)	(10)	(5)	(48)
Cyst, nasolacrimal duct	1 (2%)			
Cytoplasmic alteration, respiratory epithelium				1 (2%)
Infiltration cellular, lymphocytic, nasolacrimal duct				1 (2%)
Infiltration, glands				1 (2%)
Inflammation	1 (2%)			
Mineralization, nasolacrimal duct		1 (10%)		
Trachea	(47)	(9)	(4)	(46)
Ectasia, glands			1 (25%)	1 (2%)
Inflammation	1 (2%)	1 (11%)		

**TABLE A4****Summary of the Incidence of Nonneoplastic Lesions in Regimen A Female Mice in the 2-Year Gavage Study of Chloral Hydrate**

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
<b>Special Senses System</b>				
Eye	(41)	(4)	(5)	(40)
Degeneration, retina	1 (2%)			
Thrombus	1 (2%)			
Harderian gland	(48)	(10)	(6)	(47)
Hyperplasia				1 (2%)
Infiltration cellular, lymphocytic	18 (38%)			12 (26%)
Inflammation			1 (17%)	
Thrombus	1 (2%)			
Lacrimal gland	(41)	(6)	(4)	(40)
Atrophy	1 (2%)			3 (8%)
Infiltration cellular, lymphocytic	25 (61%)	3 (50%)	3 (75%)	20 (50%)
Zymbal's gland	(43)	(6)	(3)	(40)
Inflammation	1 (2%)			1 (3%)
<b>Urinary System</b>				
Kidney	(48)	(10)	(5)	(48)
Accumulation hyaline droplet		3 (30%)	1 (20%)	2 (4%)
Amyloid deposition, glomerulus	2 (4%)			1 (2%)
Congestion	1 (2%)			
Cyst, renal tubule	14 (29%)	2 (20%)	4 (80%)	17 (35%)
Glomerulosclerosis			1 (20%)	
Hydronephrosis			1 (20%)	
Hydronephrosis, bilateral	1 (2%)			
Infiltration cellular, lymphocytic	39 (81%)	5 (50%)	4 (80%)	38 (79%)
Inflammation	1 (2%)			
Mineralization		1 (10%)		
Necrosis, renal tubule				1 (2%)
Nephropathy	3 (6%)	1 (10%)		
Pigmentation, renal tubule			1 (20%)	1 (2%)
Polyarteritis	1 (2%)		1 (20%)	
Urinary bladder	(47)	(10)	(5)	(43)
Infiltration cellular, lymphocytic	38 (81%)	6 (60%)	5 (100%)	35 (81%)
Polyarteritis	1 (2%)		1 (20%)	